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GRADUATE SCHOOL

Thesis

NUCLEAR-SUBSTITUTED CHLOROMORPHOLINES

by

Elwood Henderson Ensor

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Approved

by

First Reader _J. Philip Mason_

Professor of _Chemistry_

Second Reader _Edw. O. Holmes, Jr_

Professor of _Chemistry_

Contents

Nuclear-Substituted Chloromorpholines

Part One

Introduction

A. Reasons leading to the choice of the problem.

Although morpholine has been known since 1889 and has been commercially available since 1935, we made the interesting observation that no work has ever been reported upon any attempted halogenation of this compound or upon the synthesis of any of its nuclear-substituted halogen derivatives. At the same time, it was noticed that among the large number of morpholine derivatives which have been prepared, there are surprisingly few in which a substituent is attached to one of the carbon atoms rather than to the nitrogen atom of the ring.

We were attracted by this problem not only because halogenation is so fundamental a step in the investigation of an organic compound, but also because of the synthetic possibilities which would be opened by an available halogen-containing morpholine. Thus in the bromination of morpholine, it was reasoned that the reaction would most likely take place according to the following scheme:
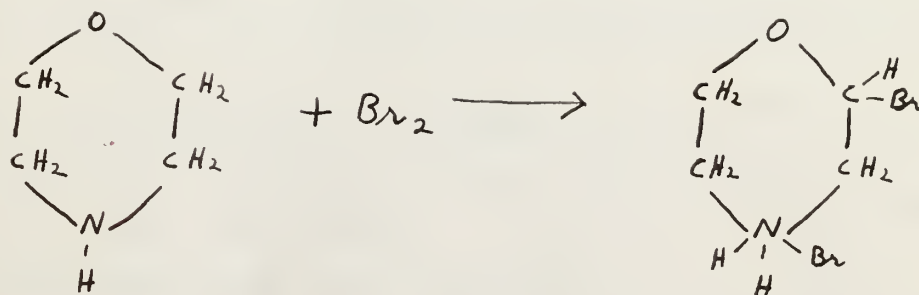
It is seen that the expected product would be an α-bromoether. This class of compounds is known to be extremely reactive so that, for synthetic purposes, it might be expected to undergo such reactions as
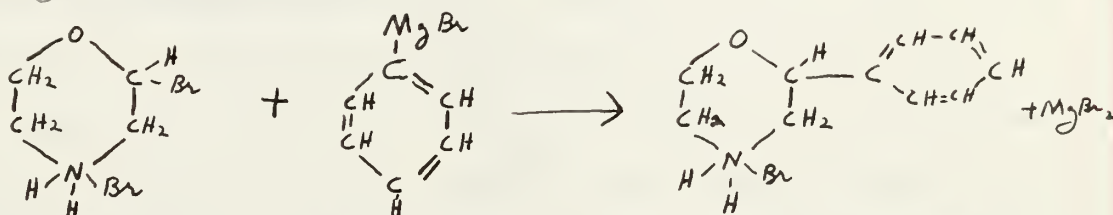
after the manner of Grignard coupling reactions investigated by Fuson (1).

This 2-phenylmorpholine (2) itself would be quite interesting because of the fact that both 4-phenylmorpholine(3),
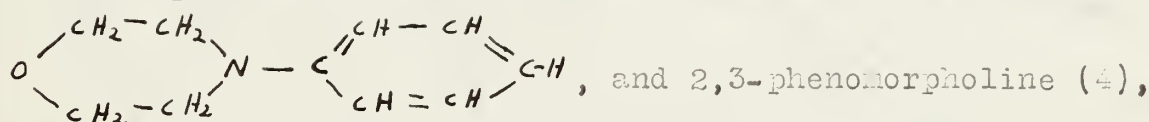
, and 2,3-phenomorpholine (4),

, have been studied.
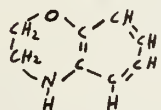
B. Discussion of some general aspects of the problem.

In spite of the many interesting rewards which the success of this reaction would offer, the possibility of its

(1). See, for example, Reynold C. Fuson, J.A.C.S., __48__, 830-36, 2681-89, 2937-42 (1926).

(2). The older method of numbering the morpholine ring by which the nitrogen atom was given the number 1 thus,   , has been replaced by the new system of nomenclature which gives the oxygen atom the number 1 thus,   .

(3). L. Knorr, Ber., __22__, 2092 (1839). Also Adkins and Simington, J.A.C.S., __47__, 1687 (1925).

(4). L. Knorr, Ber., __22__, 2036 (1839).

3.

failure was not overlooked. Thus the very fact that it had not
been reported heretofore would seem to indicate that the
reaction would be difficult if not impossible. Moreover, if
the expected α-halogenoether were actually formed, there
appeared to be a strong possibility that it would not be
stable under the conditions of the experiment. It could, for
example, obviously do one or both of two things - either
undergo further halogenation with a probable breaking down of
the ring, or polymerize according to these possible steps:

etc.
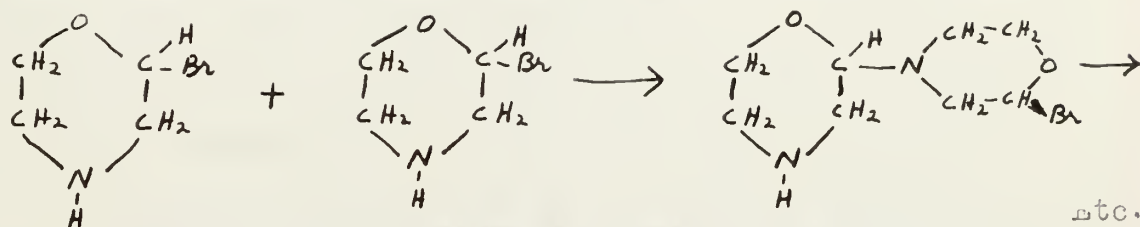
Grounds for expecting this latter reaction are
found in a statement by Henze and Murchison (5) describing
their α-chloroethers: "The α-chloroethyl ethers were found to
be extremely reactive . . . . and upon standing dry they
polymerize, forming tarry residues. Particularly noticeable
is the fact that the higher members of the series are less
stable than those of lower carbon content."

In the event of failure in direct halogenation,
several indirect methods for obtaining both the halogen
compounds and other carbon-substituted morpholines were proposed
and will be discussed in detail later.

(5). Henze and Murchison, J.A.C.S., 53, 4077-79 (1931).

Part Two

Direct Halogenation Attempts

A. Historical background to the problem.
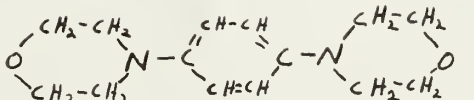
A comprehensive study of all of the existing litera-
ture on morpholine and its compounds has revealed only one
meager example in which the action of a halogen on a morpholine
compound might possibly be interpreted as yielding a halogen-
substituted morpholine. This reference is a statement made by
Knorr (6) in describing 4-ethylmorpholine in which he says,
"Bromine water gives a red-orange flocculent precipitate in
water solution, but this has not yet been studied further."
No further mention of this reaction has ever appeared.

However, it seemed to us that this reaction should
be regarded not as a true bromination reaction in the sense of
substituting a bromine for a hydrogen atom, but probably
represents merely the formation of a molecular complex. In
this respect it would be acting much like the well-known
Wagner's potassium triiodide reagent (iodine dissolved in
potassium iodide) for the precipitation and identification of
alkaloids as molecular complexes. Morpholine compounds, it
must be pointed out, are similar to the alkaloids in many
respects. Thus Wagner's reagent doesn't give a precipitate

(6). Knorr and Schmidt, Annalen, 301, 17 (1898).

with 4-ethylmorpholine or 4-methylmorpholine (7), but does
give orange-colored leaflets with morpholine(8).

Our interpretation of Knorr's red-orange precipitate
as a molecular complex finds further support in the fact that
a bromine addition product of another morpholine compound has
been reported by Axe and Freeman (9). In this case 4,4'-p-
phenylenebismorpholine, $O\begin{smallmatrix}CH_2-CH_2\\CH_2-CH_2\end{smallmatrix}N-C\begin{smallmatrix}CH-CH\\CH=CH\end{smallmatrix}C-N\begin{smallmatrix}CH_2-CH_2\\CH_2-CH_2\end{smallmatrix}O$, forms a very
intense blue addition compound with bromine much like those
formed by triarylamines and halogens.

B. Description of the first bromination of morpholine.

With such skimpy historical background, if the
above experiment can be so termed, the direct bromination of
morpholine was begun. In our first experiment, we followed
this particular procedure:

Forty-three cc. ($\frac{1}{2}$ mol) of morpholine was placed
in a 500 cc. three-neck flask and 26 cc. ($\frac{1}{2}$ mol) of bromine
was placed in a dropping funnel attached to one of the necks.
The flask was also equipped with a reflux condenser to which
was attached a gas trap, and with a motor-driven stirrer
attached to the flask through a mercury seal.

(7). Knorr and Schmidt, Annalen, 301, 18 (1898).

(8). Knorr and Schmidt, Annalen, 301, 6 (1898).

(9). Axe and Freeman, J.A.C.S., 56, 479 (1934)

The bromine was introduced very slowly because the reaction was extremely vigorous, taking place almost entirely in the vapor phase with the formation of slightly discolored yellowish-white dense gases the instant the bromine was let in. When less than ten drops of bromine had been added, a brown solid could be seen precipitating out of the morpholine. Even when the bromine was introduced very slowly, the reaction was so vigorous that the aforementioned vapors were blown up to the top of the condenser with the addition of each drop of the bromine. The fumes issuing from the top of the condenser were found to be neutral to litmus. Hence any hydrogen bromide formed must have been absorbed, as would be expected, in the reaction system.

The bromine was added over a period of three hours, and at the end of this time the flask contained a solid mass of precipitate. Consequently the reaction was stopped at this point, although only 4 cc. of the bromine had been added.

1.   Manipulation of the bromination products.

The precipitate was entirely soluble in water; and so it was dissolved in a small amount of this substance, and an estimated equivalent amount of 10% sodium hydroxide solution was added. Several attempts to extract this water solution with ether, benzene, and toluene were unsuccessful. The light yellow color of the water solution was not absorbed by the extracting liquid, and no other substance was obtained upon drying and evaporating this.

Finally it was discovered that the addition of solid sodium hydroxide pellets resulted in the appearance of an oily light brown top layer. It was found that shaking a few drops of this oil with some sodium bisulfite solution would redissolve the oil, of course, but would not remove the color, thus showing that this was not due merely to the presence of an excess of bromine.

This oil was then vacuum distilled from a 50 cc. Claisen flask whose side arm had been well vigreuxed. Almost colorless morpholine distilled over at 40^0 - 44^0 C. Twenty-seven cc. of morpholine, almost two thirds of the starting amount, was recovered in this way. However, no conclusions could be drawn from these figures because it was evident that much of this morpholine had merely been occluded in the precipitate.

After all of the morpholine had passed over, the temperature rose quickly to about $95C.$ A yellow, straw-colored liquid was collected between 95^0 and 100^0 C. Then the temperature slowly rose, and decomposition of the material in the flask began to take place with yellow-orange vapors coming over. The liquid being collected gradually became colored dark red.

There was a fairly large amount of pyrolyzed solid left in the flask after all of the liquid had distilled over.
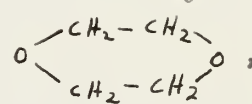
2. Investigation of the liquid obtained.

Only about one cc. of liquid was obtained in all, and this proved to be a mixture containing at least three components, a colorless liquid, a slightly higher boiling,

colored compound, and a white, easily sublimable solid. The
entire mixture was readily soluble in water and difficultly
soluble in ether.

The boiling range of this one cc. of mixture at
atmospheric pressure was $115^\circ - 135^\circ$ C., with decomposition
apparently occurring at the higher temperature. After four
careful fractionations of the mixture, a drop of the low
boiling liquid was obtained colorless, but still was not pure
as was indicated by its boiling range of $115^\circ - 122^\circ$ C.

The solid could not be obtained pure enough to take
its melting point or sublimation point because it had a
tendency to change over to an oil on standing. Extraction with
ether was tried but was unsuccessful.

In the event that the morpholine ring was broken
by bromination, a product which might be expected is ethylene
dibromide since the analogous compound dioxan, $O\big\langle {}^{CH_2-CH_2}_{CH_2-CH_2}\big\rangle O$,

breaks down on bromination to give this as the chief product
(10). However, since the original mixture was completely
soluble in water, it seemed fairly certain that no ethylene
dibromide was present. To further show that ethylene dibromide
was absent, we tried to isolate it from the higher boiling

(10). Butler and Cretcher, J.A.C.S., **54**, 2989 (1932).

fraction (11) by means of its pyridine addition product, but no such product was formed.

The remainder of both the high and low boiling fractions of our mixture was used for a qualitative test for halogens, and we were surprised to discover that no bromine was present in either fraction. A Beilstein test on a drop of the original cc. of mixture which was left in the test tube substantiated the fact that bromine was absent.

C. Description of a later bromination of morpholine.

It was obvious that the reaction would have to be carried out in a solvent medium to prevent this caking of the precipitate with its consequent occlusion of free morpholine. Several solvents were tried in varying dilution to ascertain the best reaction conditions. One of the last of these experiments will be described as typical:

Chloroform was chosen as the solvent because it is low boiling, could not be attacked by the bromine, and could not otherwise enter into the expected reaction. Forty-three cc. of morpholine ($\frac{1}{2}$ mol) was dissolved in 132 cc. of chloroform, and 25 cc. of bromine ($\frac{1}{2}$ mol) was dissolved in 25 cc. of chloroform and placed in the dropping funnel. The mechanical set-up was the same as was used in the experiment described above except that the gas trap, which had proved to be unnecessary, was omitted. The reaction was still fairly vigorous, and

(11). The boiling point of ethylene dibromide is 131° C. at atmospheric pressure.

the flask was kept in a pan of water at 10°C.

1.   Manipulation of the bromination products.

The reaction was stopped after half of the bromine had been added, and the precipitated solid was filtered out and washed with a little chloroform. The filtrate was replaced in the flask and the addition of bromine continued. This filtration of the precipitate was again carried out when half of the remaining bromine had been added. The object of this step was to get the solid out of the reaction zone so that it would be easier to see whether the theoretical amount of bromine could be used up in the reaction. It was found that almost the theoretical amount was used, but that the mixture became very red upon the addition of the last cc. or two of the bromine solution showing that this last part of the bromine was not used up.

a.   Identification of the solid product.

The various lots of solid which had been collected were purified separately by three recrystalizations from 95% alcohol. The alcohol filtrates were carefully evaporated to dryness each time and all of the solid material was collected and purified so that there would be no possibility of missing a second component of the solid if any were present. The first batch of solid was found to be much more easily purified than those later collected. When the various batches having the same melting points were combined, 55 g. of very pure solid was obtained melting at 206° - 207° C. along with 5 g. of impure material melting at 202° - 204° C. No second solid

component was present.

However, it was suspected that this solid, which consisted of beautiful white needles, might be only morpholine hydrobromide. The melting point of this compound could not be found in the literature so some was prepared from morpholine and hydrogen bromide solution. Our suspicious were substantiated when this hydrobromide melted, after recrystalization from alcohol, at exactly 205° - 207° C., and no lowering was obtained in a mixed melting point determination with my white solid. All of the solid formed in the reaction was thus shown to be morpholine hydrobromide.

b. Treatment of the liquid phases.

Next the chloroform mixture was shaken with a little water containing sodium bisulfite to extract all the bromine since this step was necessary before the chloroform solution could be fractionally distilled, such bromine-containing solutions having previously been found to pass through the best available columns as mixtures.

The water solution used for the extraction was distilled and evaporated to dryness to make certain that it had extracted nothing else along with the bromine. Only inorganic salts were obtained from this.

Finally, the chloroform was fractionally distilled using a modified Vigreux column. All of this liquid boiled between 60° and 63° C., and there was no residue. Hence the morpholine hydrobromide was the only product which could be isolated from this experiment.

2.   Discussion of the numerical results.

It is rather interesting to look over the actual figures of this experiment for a moment.   It can easily be calculated that the 50 g. of morpholine hydrobromide obtained represents a 70 % yield of this compound from the morpholine taken at the start of the experiment.   Thus 30 % or 13 g. of our morpholine remains unaccounted for.   Obviously the hydrogen to form our morpholine hydrobromide must have come from these 13 g. of morpholine.   It is also an evident fact that the hydrogens on the carbon atoms of the morpholine must have been attacked because to furnish enough hydrogen to give this much of the morpholine hydrobromide, this 13 g. of morpholine must have furnished .36 g. of hydrogen.   When the calculation is made, it is found that this represents an average of two and one half atoms of hydrogen from each molecule of this 13 g. of morpholine.

These figures have shown thus that each molecule of morpholine reacts with two or three equivalents of bromine, not just one as had been hoped.

Now if this reaction were merely one of bromine substitution into the morpholine ring without any degredation of this ring, we would expect almost certainly to get products containing this bromine which would boil higher than 100° C. at least.   The fact that no such products were present is pretty good proof that the ring was destroyed.

The only alternative to this conclusion is to assume the formation of an unsaturated compound thus:

Further reaction might analogously yield some oxazine,
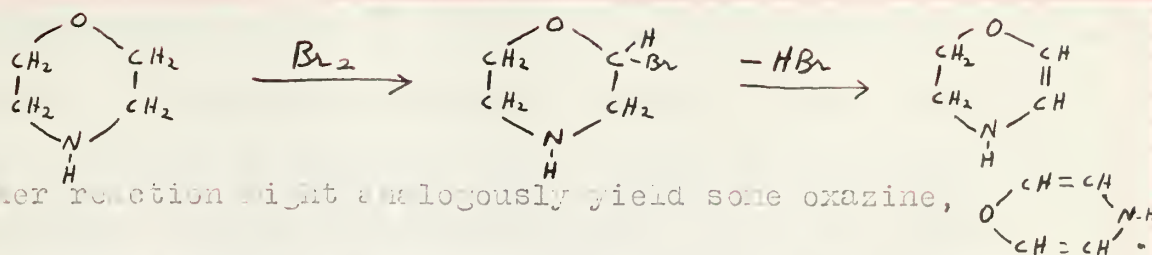
However, such assumptions are not tenable for two reasons.
First oxazine has been made during the course of this research,
as will be discussed later, and has been found to have a boiling
point of 106° - 111° C. Hence these compounds also would have
higher boiling points than 100° C.; and so should have been
isolated. Secondly, it has been shown above that the conditions
of the experiment were so controlled that there was a slight
excess of bromine present in the reaction vessel at the end of
the experiment. Under these conditions it is extremely improb-
able that these unsaturated compounds could exist in this
solution as such.

Hence it is conclusive that this bromination has
broken the morpholine ring and torn and oxidized it to small
or gaseous fragments that could not be isolated or identified.

D. Stability of the morpholine ring.

That such a splitting of the morpholine ring is
quite possible is shown by work done by others on the stability
of this system. Thus Knorr (12) states that while morpholine
is indifferent towards water at 200° C., 10% sodium hydroxide
at 160° C., concentrated hydrochloric acid at 160° C., and

(12). L. Knorr and Schmidt, Annalen, 301, 17-18 (1893).

phenylhydrazine at 200 C°., it undergoes slow oxidation with acid
solutions of potassium permanganate which becomes more rapid
in the presence of alkalies. The product was not isolated or
identified. We see therefore that the morpholine ring is
attacked by oxidizing agents, and, of course, it should be
pointed out that the halogens are pretty good oxidizing agents,
bromine itself being just a slight bit weaker than acid
potassium dichromate as an oxidizing agent and stronger than
ferric chloride (13).

A much more elaborate experiment on the stability
of the morpholine ring was carried out by von Braun and
Köhler (14). These authors studied the effect of the Hofmann
exhaustive methylation reaction and of cyanogen bromide, CNBr,
on the tertiary base, 4-methylmorpholine.

With cyanogen bromide, instead of the usual von
Braun reaction (15) in which methyl bromide would have been
split off, the morpholine ring was broken thus:

$$\begin{array}{c}
O \\
CH_2 \quad CH_2 \\
CH_2 \quad CH_2 \\
N \\
CH_3
\end{array} + CNBr \longrightarrow CH_3\text{-}\underset{CN}{N}\text{-}CH_2CH_2OCH_2CH_2Br.$$
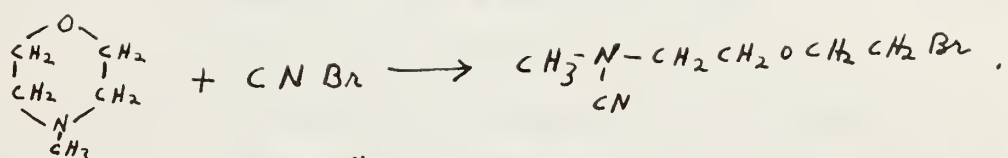
Von Braun and Köhler came to the conclusion that, of
the list of cyclic bases they studied, morpholine stands
with tetrahydroisoquinoline and dihydroisoindole at the bottom

(13). H.I. Schlesinger, "General Chemistry", page 177. (1934 Ed.)
(14). J. von Braun and Z. Köhler, Ber., 51, 250-55 (1918).
(15). F.C. Whitmore, "Organic Chemistry", page 540. (1937 Ed.)

of the list (16) as the ones most easily ruptured by cyanogen

bromide. Also morpholine stands between these two in

stability towards exhaustive methylation, these three again

standing at the bottom of the list. (17)

E.   4-Acetylmorpholine.

Although there seems to be little doubt that the ring

is torn apart in the bromination of morpholine itself, it is

possible that a morpholine derivative could be found which

would halogenate without breaking the ring. Von Braun's work

mentioned above on 4-methylmorpholine would indicate that such

would probably not be the case, but not wishing to overlook

this possibility, we decided to try the halogenation of some

morpholine derivative.

In choosing a derivative to work with, we wanted one

which could easily be hydrolized back to a morpholine derivative

in which the nitrogen atom would be unsubstituted after some

radical, like, for example, our suggested phenyl group, had been

attached to one of its carbon atoms. At the same time we

wished to protect the imino group as much as possible since this

(16). The complete list, in order of stability towards CNBr, is
       tetrahydroquinoline > piperidine > pyrrolidine >
       dihydroindole > tetrahydroisoquinoline
                         dihydroisoindole
                         morpholine

(17). The complete list, in order of stability towards the
       Hofmann reaction, is {tetrahydroquinoline > piperidine >
                             dihydroindole
       pyrrolidine > dihydroisoindole > morpholine > tetrahydroiso-
       quinoline.

has been indicated as being the probable first point of attack
in the degradation of the ring. For this, 4-acetylmorpholine was
first chosen in the hope that the following synthesis could be
carried out:
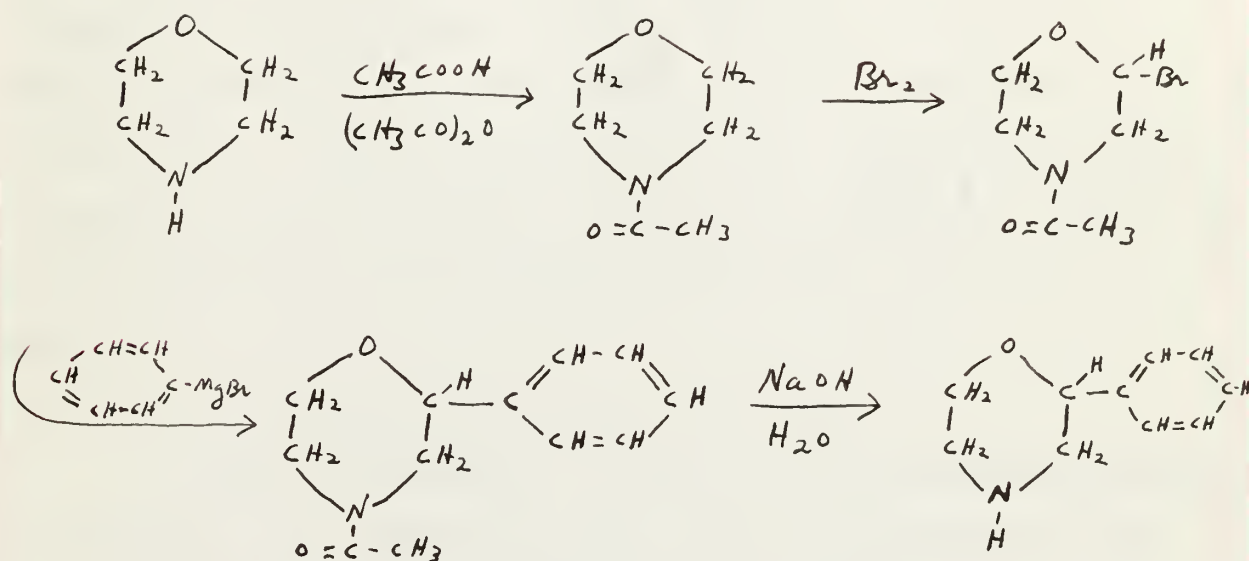
The acetyl derivative would have the further advantage
of being a neutral compound; and hence we would not be incon-
venienced by the intermediate formation of the hydrogen bromide
salt.

1. Preparation of the 4-acetylmorpholine.

The acetylation of morpholine was very easy. Forty-
four cc. of morpholine was treated with a mixture of 50 g. of
acetic anhydride and 50 g. of glacial acetic acid, refluxed
for 30 minutes, and distilled. The portion boiling above 200° C.
was collected, and upon a redistillation of this, 56 g. (50 cc.)
of 4-acetylmorpholine was obtained. The yield was 86 %.

2. Properties of the 4-acetylmorpholine.

The 4-acetylmorpholine was a colorless, almost

odorless liquid. Its boiling point was 239°C. (uncorr.) as compared with 238.5° - 238.9°C. (uncorr.) reported in the literature by Louis Médard (18).

We were interested to find out that this compound is a liquid at room temperature (19). The suggestion was made that it might prove to have valuable solvent properties since the analogous compound acetamide is a most excellent solvent, but is inconvenient because it is a solid below 81°C. The solvent properties of 4-acetylmorpholine have never been studied.

3.   Bromination of 4-acetylmorpholine.

When we attempted to brominate our 4-acetylmorpholine, we found that no bromination took place, as indicated by the fact that no heat was liberated, and that the bromine color did not disappear from the chloroform solution. Several of the usual halogenation catalysts were tried, including iodine, iron, and antimony, but without success. Finally we seemed to get some reaction using red phosphorous as a catalyst. However, the only product was a small amount of a dark red amorphous solid which became an oil on standing in a desiccator. On trying to recrystalize this solid from hot alcohol, it was discovered that this mixture was quite lachrymatory.

The possibility of bromination taking place in the

(18). Louis Médard, Bull. soc. chim., [5] 3, 1343-4 (1936).
(19). Its melting point is 14°C. according to Médard (18).

acetyl group had, of course, been an obvious disadvantage in the use of this compound from the start. Moreover, one of the characteristics of compounds containing a halogenated acetyl group is that they often are lachrymators. This indication that our 4-acetylmorpholine had brominated in the acetyl group rather than in the morpholine ring together with the nature and low yield of the product were enough to persuade us to abandon this compound and try to find a more suitable one.

F. Trichloroacetylmorpholine.

The next approach to the problem which suggested itself was to use trichloroacetylmorpholine and chlorination in place of bromination. Trichloroacetic acid was available for a starting material, but since it was quite possible that morpholine could react with the chlorine atoms here, it was thought best to use the acid chloride. However, in several attempts to prepare this compound, much difficulty was encountered. Moreover, a much more suitable compound had meanwhile been suggested, so it was decided to use this in place of the trichloroacetylmorpholine.

G. Use of 4-Nitrosomorpholine.

The apparent advantages of this new compound, 4-nitrosomorpholine, were several; it could be more easily prepared, it would be a neutral compound, and it could be hydrolized easily in an acid medium.

1. Preparation of 4-nitrosomorpholine.

Our 4-nitrosomorpholine was prepared according to

the directions of Knorr (20) with some slight variations.
Twenty-six g. of morpholine was added to an equal mass of
water, and 25 g. of 50% sulfuric acid (21) was introduced.
After cooling well, 33 g. of sodium nitrite was dissolved in
120 cc. of water, and this mixture was added to the morpholine
solution. Dilute sulfuric acid was added drop by drop until
an appreciable yellow, oily top layer had appeared. This was
extracted with ether, more dilute sulfuric acid was added until
another oily layer appeared, this was extracted with ether,
and this whole process was repeated until the second layer no
longer was formed upon the addition of dilute sulfuric acid.
The reason for this rather laborious and time consuming series
of extractions was that much of the 4-nitrosomorpholine is
hydrolyzed by using an excess of the acid as Knorr does.

2. Properties of 4-nitrosomorpholine.

After drying over potassium hydroxide, the solvent
was **evaporated off**, and the compound was distilled at
atmospheric pressure. It was found to boil at 225° C., thus
comparing favorably with Knorr's (20) boiling point of 224-
224.5° C. at 747 mm. The yield of the yellow 4-nitrosomorpholine
was 32.5 g. (94%).

(20). L. Knorr, Annalen, 301, 6 (1898).

(21). We also tried HCl, but found that it could not be used
     safely, for a very slight excess of this acid hydrolyzes
     the 4-nitrosomorpholine back to morpholine rapidly. This
     effect is much less pronounced when H_2SO_4 is used.

3.   Chlorination of 4-nitrosomorpholine.

Upon chlorinating 10 cc. of this 4-nitrosomorpholine in a chloroform solution without a catalyst, a surprising and unexpected result was obtained. The only product isolated in this case was morpholine hydrochloride, which, when crystalized from hot alcohol, melted at 175°- 176°C. as compared with the melting point of 174°- 177°C. given by Knorr (22) for this substance. As proof of its composition, some pure morpholine hydrochloride was prepared, and no lowering was observed when a mixed melting point was taken with this and our compound.

Since careful precautions had been taken to exclude all water from the reaction, this result can only be explained by the assumption that the necessary hydrogen atom was obtained from some of the 4-nitrosomorpholine molecules. Thus, just as in the case of the bromination of morpholine itself, the first step in the reaction must have been the substitution of a chlorine for a hydrogen atom in the 4-nitrosomorpholine. The hydrogen bromide formed by this reaction then hydrolyzed the nitroso group from the 4-nitrosomorpholine to form the morpholine hydrochloride which precipitated from the reaction zone. The halogen molecules must then have been further reacted on and, as in the former reaction, transformed into small fragments which could not be identified or isolated.

(22). L. Knorr, Annalen, 301, 4 (1898).

Part Three

Indirect Methods

A. Payman and Piggott's use of such methods.

After the experiments described above, it seemed rather conclusive that direct halogenation was impossible, and that indirect methods would have to be used to obtain a halogenated morpholine or a morpholine with a substituent in the 2, 3, 5, or 6 position.

Carbon-substituted morpholines are not unknown for a very few of these have already been made by indirect methods. Thus, for example, Payman and Piggott have patented (23) the following synthesis for carbon-substituted morpholines:

[Chemical reaction scheme: A methyl-substituted aromatic ring bearing SO_2NH_2 reacts with $2\ Cl\text{-}CH\text{-}CH_2OH$ (with CH_3 substituent), warm, to give a ring bearing $SO_2N(CHCH_2OH\cdot CH_3)_2$. Then H_2SO_4, $160°\text{-}200°C$, gives a sulfonamide with a morpholine-type ring; then H_2SO_4 / H_2O gives a ring bearing SO_3H plus 2,6-dimethylmorpholine.]
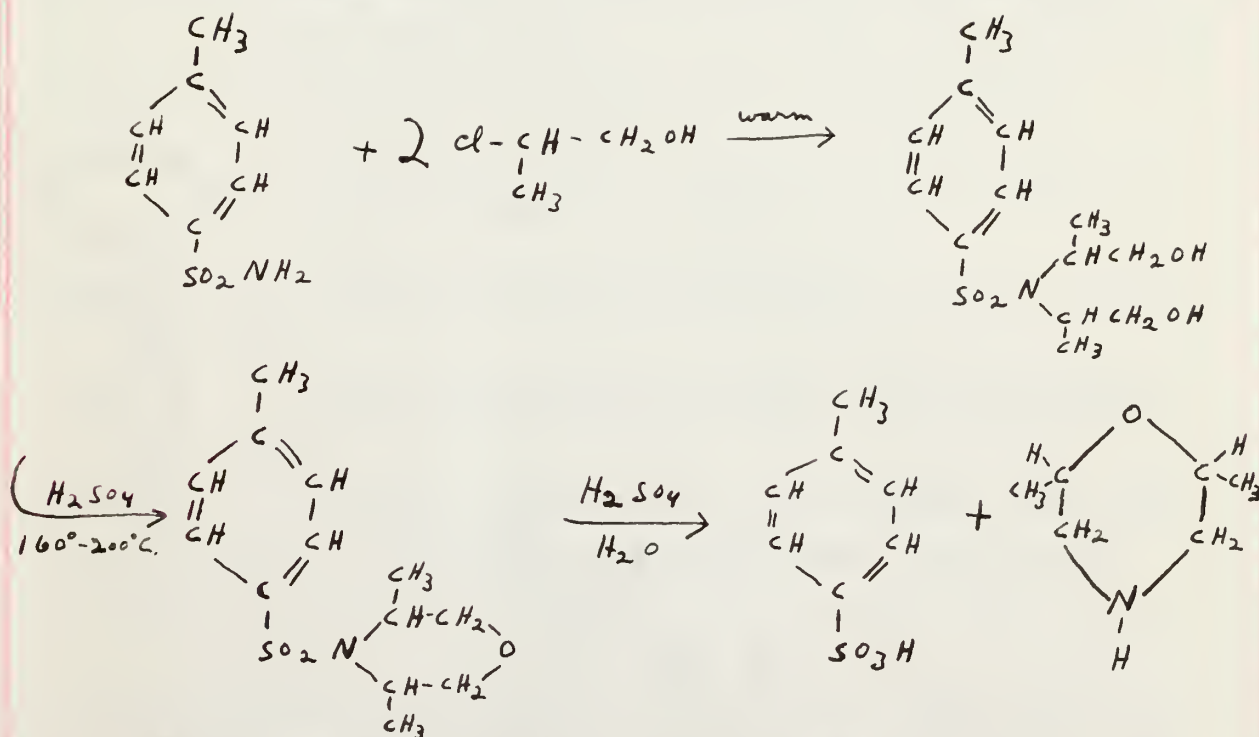
(23). British patent 293,336 (1927), German patent 520,156, and United States patent 1,359,527.
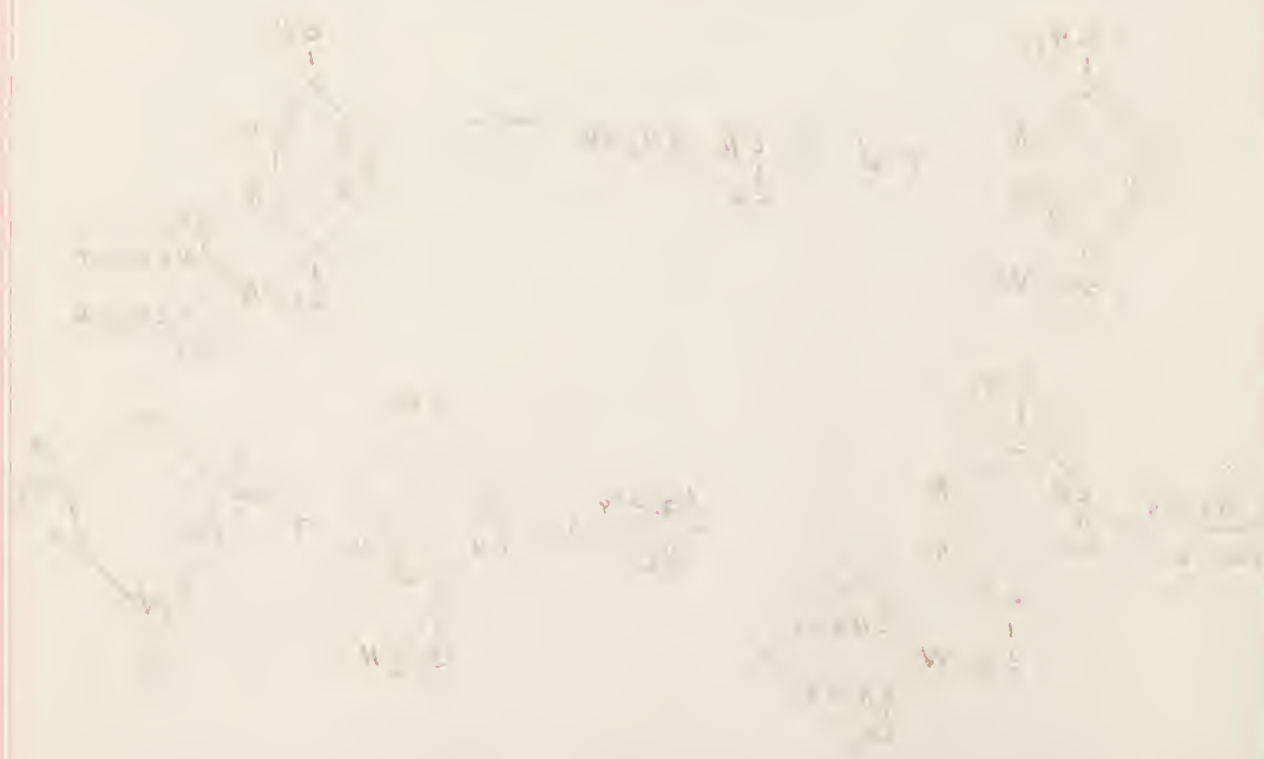
This 2,6-dimethylmorpholine was obtained in 30%
yield and described as a colorless liquid boiling at $145^\circ C$.
under atmospheric pressure. It is a very strong base with an
ammoniacal odor. It is soluble in water in all proportions
and could be salted out of its concentrated water solution by
solid sodium hydroxide. It was said to be useful in the
vulcanization of rubber.

However, this synthesis could not be used to prepare
carbon-substituted chloromorpholines by substituting, for

example, $Cl-\underset{Cl}{CH}-CH_2OH$, for the propylene chlorohydrin used

in the above illustration. Payman and Piggott specifically
point out in their United States patent that, "This invention
refers to a new method for manufacture of morpholine,

 , its homologues and derivatives; that is, the

production of compounds having the following general formula:

 wherein R_1, R_2, R_3, and R_4 represent
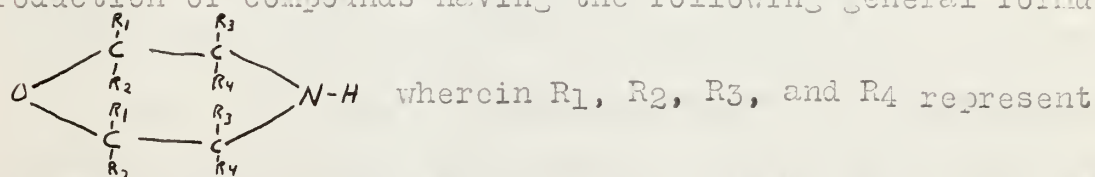
hydrogen or substituent groups other than halogen. The new
process comprises condensing a β-hydroxy-α-halogenated
derivative of ethane or a homologue of the same; that is, a

compound of the general type, $X-\underset{R_2}{\overset{R_1}{C}}-\underset{R_4}{\overset{R_3}{C}}-OH$ wherein R_1, R_2,

R_3, and R_4 represent hydrogen or substituent groups other
than halogen."

B. Oxazine.

The simplest indirect approach to our problem of making a chloromorpholine would appear to be the addition of hydrogen chloride or chlorine to the unsaturated compound oxazine, $O\overset{CH=CH}{\underset{CH=CH}{\diagup\diagdown}}N-H$. The first difficulty which arose here, however, was the fact that, while oxazine had been given its name, it was still an unknown compound (24). We therefore set about to see whether oxazine could be made by the dehydrogenation of morpholine using selenium as the dehydrogenating agent.

1. Low-temperature preparation of oxazine.

Upon looking up this type of reaction in the literature, it was found that the usual conditions followed consisted of mixing the selenium with the saturated compound and heating the mixture for 36-48 hours at $250^{\circ} - 400^{\circ}$ C. Since in the case of morpholine, whose boiling point is 128.3° C., such high temperatures would have to be attained in a glass or, preferably, a steel bomb tube, we decided to see whether or not a very long reaction time could be substituted for these high temperatures.

(24). We learned from Dr. Robert K. Summerbell of Northwestern University that he has isolated an unpleasant-smelling liquid from the reaction of a palladium-activated charcoal catalyst on morpholine which he believes to be oxazine, but he sent us none of the physical properties of this compound.

Forty-three cc. ($\frac{1}{2}$ mol) of morpholine was mixed with 80. g. (1 mol) of selenium in a 500 cc. round bottom flask. The flask was equipped with a reflux water condenser and heated to 125°- 130° C. with a hot plate. The system was kept at this temperature for 336 hours (2 weeks).

a. Manipulation of the products.

After cooling, the selenium was shaken five times with 50 cc. portions of ether. The organic material was then further extracted by shaking the selenium with 100 cc. of ether in the shaking machine overnight.

The ether extracts were combined and filtered. This solution was colored a reddish brown, but this proved to be due to colloidally dispersed selenium and not to the presence of any organic compound.

After the solvent was distilled off, the temperature rose quickly to 100° C., and gradually continued to rise. The fraction boiling up to 121° C. was put aside, and a much larger fraction boiling between 121° and 128° C. was collected. These fractions were almost colorless, the second fraction having become slightly yellow when prolonged distillation forced over a few drops of a yellow liquid. The residue in the flask contained only a few drops of yellow liquid, some deposited selenium, and a few particles of white solid which had formed. It was suspected that this solid and colored liquid were polymerization products of oxazine.

These two fractions were redistilled six times using

various types of fractionating columns. Fifteen cc. of pure morpholine boiling between 127° and 128.5° C. and having a refractive index of 1.4533 at 22° C. was obtained along with 1.5 cc. of a colorless liquid boiling between 103° and 109° C.

b. Identification of the low boiling fraction.

Several facts made us suspect that this low boiling fraction was not the pure oxazine which we had hoped to get in this experiment, but that it rather consisted of a mixture which could not be separated by ordinary fractionation. In the first place, morpholine is a fairly hydroscopic substance (25), and it is quite difficult to separate small amounts of water from morpholine by fractionation. It seemed quite probable that the morpholine used in this experiment should have absorbed some water during its long period of refluxing. Hence we expected this 1.5 cc. of low-boiling liquid to contain some water and morpholine. However, the presence of a third compound in this fraction was indicated by the fact that some of the colored liquid and white solid mentioned above was formed during each distillation of this low-boiling fraction. This is, of course, never obtained during a distillation of pure morpholine. The formation of these substances would seem to conform with the idea that oxazine was present in this mixture, and that this colored liquid and white solid were polymers of this compound formed under

(25). Wilson, Ind. Eng.Chem., 27, 867-71 (1935).

the influence of the high temperature (26). Finally it was
observed that this liquid discolored an alkaline potassium
permanganate solution much more rapidly than does morpholine.

Our chief reason for believing this low boiling
fraction to be a mixture was that, although its boiling
range did not change, its refractive index decreased considera-
bly with each distillation. Moreover its numerical value
always remained between those of morpholine and water (27).
The value of the refractive index of this mixture was 1.4164
after its sixth distillation. Its specific gravity at 20°C.
was 1.041, higher than that of morpholine or of water.

Since only 1.5 cc. of this mixture was available, it
would have been a very difficult job to separate it into its
pure components and identify these, so the following experiments
were devised to show its qualitative composition:

To 10 drops of the mixture in an evaporating dish was
added one cc. of benzoyl chloride. The evaporating dish was
covered with a watch glass and evaporated to dryness on a
steam bath. When this evaporation was complete, the under
side of the watch glass was covered with a white solid which
had sublimed from the mixture. This solid was shown to be
pure benzoic acid; and so it proved the presence of water in
the mixture since it must have been formed by the reaction

(26). The oil bath usually rose as high as 170°C. when
distilling the mixture through a column.

(27). The refractive index of water at 20° is 1.3333.
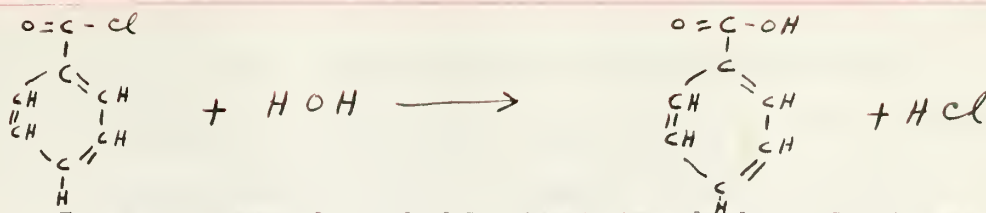
It also seemed probable that the hydrochloric acid liberated in the above reaction should form a salt with the morpholine or oxazine present. Hence the solid in the evaporating dish was washed well with ether to remove any benzoic acid remaining in it, and was then recrystalized from hot absolute alcohol. The solid obtained was white and extremely soluble in water. It melted at 174° C. and was shown to be morpholine hydrochloride.

The presence of a third component in the low-boiling mixture was shown by dissolving the remaining portion of this liquid in 2 cc. of water, adding 1 cc. of benzoyl chloride, and then several 1 cc. portions of 10% sodium hydroxide solution with vigorous shaking. Much heat was given off by the reaction and a precipitate was formed which was insoluble in hot water. Since benzoic acid is soluble in hot water and benzoylmorpholine is easily soluble in water, this precipitate[23] must have been formed by a reaction of the benzoyl chloride with something in the mixture other than morpholine or water. This solid was very soluble in alcohol and melted with decomposition above 300° C.

c. Discussion of the experiment.

The experiments described above do not definitely

(23). Knorr, Annalen, 301, 7 (1898).

prove that oxazine was formed by the action of selenium on morpholine, but they do show that some compound was produced in very low yields which forms a benzoyl derivative upon treatment with benzoyl chloride and colored products upon heating for several minutes at 170° C.

2. High-temperature preparation of oxazine.

In an attempt to obtain an appreciable yield of oxazine for our work, we decided to try to dehydrogenate morpholine with selenium in a glass bomb tube at temperatures above 200° C.

One disadvantage of this method of preparation became apparent from the start; not more than 10 cc. of morpholine could be placed in one of the tubes at the beginning of an experiment because the pressure created at 200° C. by larger amounts of morpholine vapor easily burst the tube.

Moreover we soon found that the reaction of morpholine with selenium did not take place to any appreciable extent when one of these bomb tubes was heated at 200° - 230° C. for 36 - 48 hours. Upon opening the tube after this treatment, no pressure was observed and nothing but morpholine was obtained when the liquid was fractionated. However, there was some odor of hydrogen selenide, indicating that a trace of the morpholine had been dehydrogenated.

When the tubes were heated to 245° C., they usually exploded violently after one or two hours of heating. The strong garlic-like odor of hydrogen selenide filled the room

and all indications seemed to point to the fact that dehydrogenation of the morpholine occured to an appreciable extent at this temperature.

After several attempts and explosions, a bomb tube was obtained which did not burst at 245° C., and this was heated at 245° - 260° C. for 44 hours. It was allowed to cool for 24 hours, and there was a considerable amount of pressure in the tube when it was opened. The unmistakable odor of hydrogen selenide showed that dehydrogenation must have taken place.

The liquid in the tube was extracted well with ether, filtered, and fractionated using a Vigreux column. After all of the solvent had distilled off, only a drop or two of liquid was obtained boiling below 110°c. No morpholine fraction at all was obtained, and the temperature rose quickly to 190°c. where a little dark red liquid began to distill with much decomposition. The distillation was stopped at this point, and the apparatus was modified for vacuum distillation in an attempt to avoid much of this decomposition by using lower temperatures. However, the decomposition continued in spite of these precautions when the distillation began so that only a few ccs. of a red liquid boiling between 130° and 170° C. under 25 mm. pressure was obtained.

It was thought at first that this liquid consisted of a mixture of polymers of oxazine formed under the influence of the high temperature - an hypothesis which would agree

quite well with our former observations (29). However, in
view of the facts that a Kjeldahl nitrogen determination
showed that this mixture contained only 12% nitrogen instead
of the 16.3% nitrogen which a true polymer of oxazine would
contain, and that a molecular weight determination showed its
average molecular weight to be about 225, it seemed more
accurate to believe that the mixture consists of both polymeri-
zation of the oxazine formed and a partial pyrolysis of these
products.

It was thought that a neutralization equivalent of
this product would have thrown some light upon the mechanism
of this polymerization, for if this had been the same as that
expected for oxazine, it would indicate that polymerization
had taken place through the double bonds. However, it was
impossible to find this value because the deep orange color
of an aqueous alcohol solution of this polymer completely
obscured the color of any indicator used for the titration.
Moreover, the presence of pyrolysis products in the polymer
mixture would greatly lessen the worth of a neutralization
equivalent. This polymer mixture formed no benzoyl derivative
with benzoyl chloride.

3.   Arnold and Collins' method of dehydrogenation.

From the above experiments it was obvious that

(29) See page 25

selenium was an entirely unsatisfactory reagent for the
dehydrogenation of morpholine because when low temperatures
were used, a negligible yield of oxazine was obtained, and
when high temperatures were used, the oxazine formed
immediately polymerized. A low temperature method of dehy-
drogenation was needed; and so when Arnold and Collins (30)
described such a method using chloranil as the dehydrogenating
agent, we decided to try this. In this method the equation
for the reaction we hoped to obtain would be as follows:
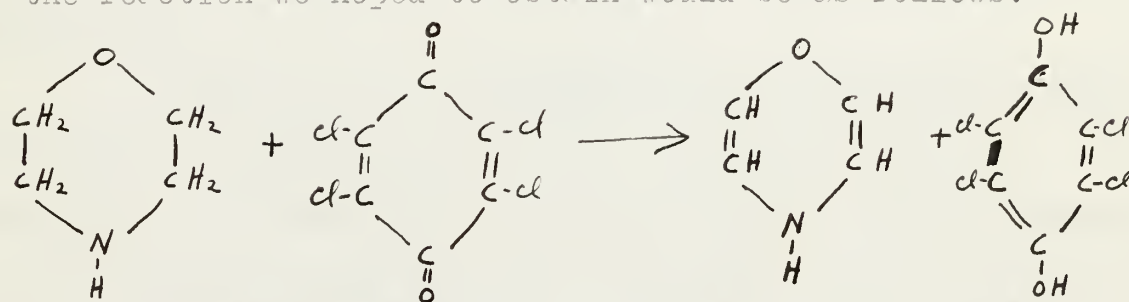
    The reaction was said to take place in boiling
xylene solution at 140 C. Much of the hydroquinone formed
could be recovered by cooling the xylene solution.

    However, this method was found to be inapplicable to
the dehydrogenation of morpholine, for instead of this reaction
occurring, the morpholine reacted immediately with the chlorine
atoms of the chloranil. No hydroquinone could be isolated
from the mixture on cooling.

    We sought to avoid this undesirable reaction by
using acetylmorpholine in place of morpholine. However, we
were surprised to find that here again the chlorine atoms in

(30). Arnold and Collins, J.A.C.S., 61, 1407 (1939).

the chloranil entered into some reaction with the acetylmor-
pholine with the evolution of a copious amount of hydrogen
chloride. In this case the reaction was much slower, occurring
only upon long boiling of the mixture, but again no unsaturated
product and no hydroquinone could be isolated.

C. A proposed Boord synthesis of chloromorpholine.

Our inability to obtain a supply of oxazine caused
us to turn our attention to some other possible indirect
methods of obtaining chloromorpholine or carbon-substituted
morpholines.

A recent paper by Filachione (31) describing a new
synthesis of chloroacetal made this expensive chemical
available at low cost and in large amounts, and made attractive
several suggested syntheses which required this as a starting
material.

1. The similarity of our synthesis to that of Boord.

The essential step of the most interesting of the
methods of synthesis of a chloromorpholine which we considered
consists of the adaptation of Boord's synthesis of $\measuredangle$- chloro-
ethers (32) to a cyclic ether. To clarify this step, let us
review the steps of Boord's synthesis briefly. Here an alcohol

(31). Edward M. Filachione, J.A.C.S., 61, 1705 (1939).

(32). Swallen and Boord, J.A.C.S., 52, 354 (1930).
Dykstra, Lewis, and Boord, ibid., 52, 3397-3400 (1930).
Shoemaker and Boord, ibid., 53, 1507-8 (1931).

and an aldehyde are mixed, cooled to 0° C., and dry hydrogen
chloride gas is passed into the mixture. The first step in the
reaction is undoubtedly the formation of a hemiacetal, but this
is not isolated, for the hydroxyl group is replaced immediately
by a chlorine atom as indicated to give us our desired
α - chloroether. The reactions may be represented:

$$C_3H_7-\overset{H}{\underset{}{C}}=O + C_2H_5OH \xrightarrow[0^\circ C.]{dry\ HCl} \left[C_3H_7-\overset{H}{\underset{OH}{C}}-OC_2H_5 \right] \xrightarrow{HCl} C_3H_7-\overset{H}{\underset{Cl}{C}}-OC_2H_5$$
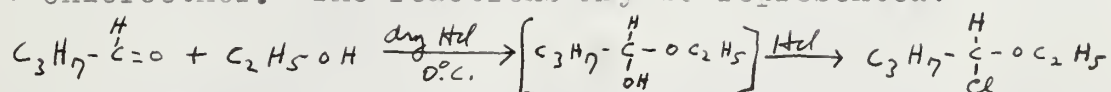
The last step of our proposed reaction is precisely
the same as this except that our alcohol and aldehyde groups
are the end groups of a single molecule instead of being the
functional groups of separate compounds. Our complete reaction
is as follows:
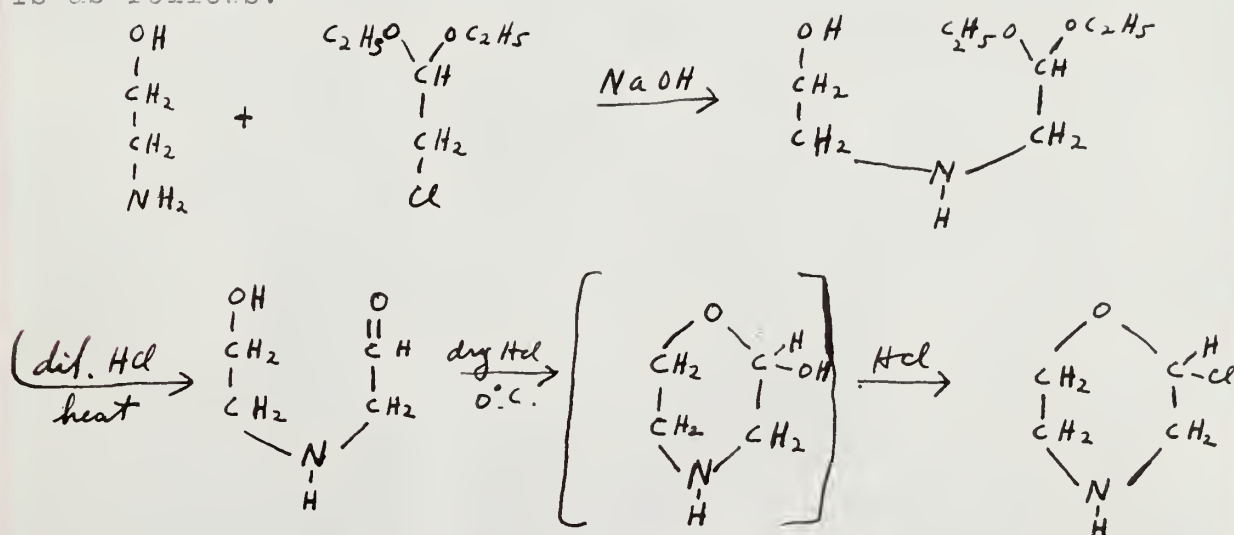
This experiment, if it could be performed as indicated,
would have the great advantage of simultaneously proving the
position of the chlorine atom in our product by the very
nature of the synthesis.

We originally believed that two extra steps would
have to be added to our synthesis as we have represented it
above - namely, that of protecting the hydroxyl group of the

β - aminoethanol with an acetyl group so that the amino group
and not this hydroxyl group would react with the chloroacetal,
and that of hydrolyzing this acetyl group off after it had
served its purpose. However, an examination of the literature
revealed no instances in which the amino group did not react
entirely in preference to the hydroxyl group in such cases, so
that the introduction of an acetyl group was considered
superfluous and unnecessary.

    2.   Preparation of the starting materials.

        a. β-aminoethanol.

        The β-aminoethanol needed in this experiment was
available, and was merely purified by a distillation, the
portion boiling at 169-171° C. being used.

        b. Chloroacetal.

        We prepared our chloroacetal by Filachione's (31)
method. The steps involved in this synthesis include:

$$CH_3-\overset{O}{C}-O-CH=CH_2 + Cl_2 \xrightarrow{\text{dry ice}} CH_3-\overset{O}{C}-O-\underset{Cl}{CH}-\underset{Cl}{CH_2}$$

$$\xrightarrow{C_2H_5OH} \underset{C_2H_5O}{\overset{C_2H_5O}{>}}CHCH_2Cl + CH_3\overset{O}{C}-OC_2H_5$$
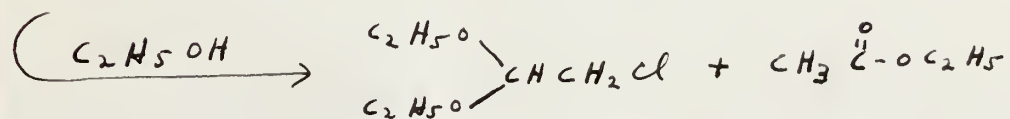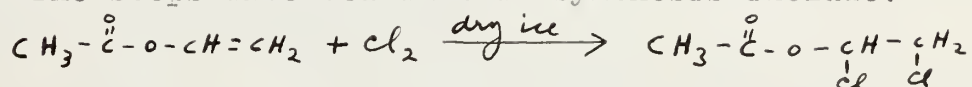
        The actual experiment may be described thus: The
calculated amount of chlorine was passed through a flowmeter
into a solution of 92g.(2 mols) of absolute alcohol and 43g.
of vinyl acetate ($\frac{1}{2}$ mol) which had previously been purified by
distillation of the commercial material. The entire addition
of the chlorine took about four hours, and during this time the
alcohol solution was cooled by dry ice in acetone. This
solution remains colorless during this addition of chlorine as

long as it is well cooled. However, if the solution is not sufficiently cooled it becomes yellow, and the chlorine acts as an oxidizing agent instead of merely adding to the double bond as desired. It was noticed that this same yellow color appeared during the addition of the last few ccs. of the calculated amount of chlorine, and that the color disappeared when the flask was shaken. The similarity of this color appearance to the change in the color of an indicator during a titration led us to believe that this may function as a good indication as to when the reaction is complete.

The mixture was allowed to set overnight since the alcoholysis of this dichlorovinylacetate is a slow reaction. The next morning the mixture was poured into water, and the chloroacetal settled out on the bottom as a colorless layer. It was extracted with ether, washed free of acid with water, and dried with calcium chloride.

After the solvent was evaporated off, the liquid was distilled in vacuo. A redistillation of the products at 21 mm. pressure gave us 5 g. of material boiling below 43°C. and 53 g. of chloroacetal boiling between 62° and 64°C. Its refractive index at 24°C. was 1.4163. These constants agree quite well with those of Filachione who gives the boiling point of chloroacetal as 53° - 54°C. at 16 mm. and its refractive index as 1.4171 and also with Eastman's catalogue of organic chemicals which lists chloroacetal as boiling between 62° and 64° at 20 mm. pressure. Our yield was 70% as

compared with the 33% claimed for this process.

3.   Second step in the synthesis.

a.   Description of the experiment.

Much difficulty was experienced in the second step of this synthesis. The correct conditions for carrying out this reaction have not yet been found although a number of different solvents and combinations of solvents have been tried.

It was thought at first that water would be the best solvent. After the aminoacetal had been formed, dilute hydrochloric acid could be added, the solution boiled to hydrolyze the acetal, and the aldehyde isolated as the 2,4-dinitrophenylhydrazone, the oxime, or the sodium bisulfite derivative.

This method has the disadvantage of giving us a heterogeneous reaction mixture because the chloroacetal is not soluble in water. At the same time this means that there will always be an excess of the β-aminoethanol in the reaction zone so that the probability of getting two molecules of chloroacetal reacting with one molecule of β-aminoethanol would be lessened.

Five cc. of the chloroacetal was added to a water solution of 15 cc. of β-aminoethanol. The water solution gradually turned yellow, then brown, and finally a very dark reddish brown. The chloroacetal layer disappeared only after two days of refluxing. Dilute hydrochloric acid was then added in excess and the solution boiled for 30 minutes. However, after this no aldehyde could be isolated from this

water solution, although a definite reaction was obtained with sodium bisulfite as shown by the heat liberated when this solution was added. This, of course, proves nothing because whether or not the β -aminoethanol reacted with the chloroacetal as we expected, there would still be an aldehyde in the solution, formed by the hydrolysis of the chloroacetal.

b. Difficulties encountered.

No precipitates were obtained with hydroxylamine or 2,4-dinitrophenylhydrazine either. Moreover, these reagents have disadvantages of their own. Thus if the sodium bisulfite addition product were formed, the aldehyde would have to be regenerated in water solution so that the net result would be only a concentration and purification of the aldehyde, and the problem of its isolation in the free state would remain unsolved. Of course, distillation or ether extraction may be possible from this concentrated solution. Moreover, in the case of the 2,4-dinitrophenylhydrazine, regeneration of the aldehyde is successful in only a very few cases according to Allen and Richmond, the discoverers of this reagent (33).

Accordingly we tried to prepare the nitroso derivative of this iminoaldehyde in the hope that it would be water insoluble, and would separate out. However, this didn't appear to be the case because no second layer was formed.

(33). Allen and Richmond, Journal of Organic Chem., 2, 225 (1937).

c. Conclusions.

Because of these difficulties this synthesis was not continued beyond this point according to the steps which we had planned, but a new line of attack was devised for the problem as we will describe later(34). However, two facts should be pointed out in connection with this synthesis before turning our attention to its later developements:

(1.) The reaction is a very slow one as we showed in two ways - by the length of time it took the chloroacetal layer described in the above experiment to disappear, and by running the reaction in an alcohol-ether mixture. In this mixture both of the reagents are soluble and react slowly to give the usual dark solution, but by adding an excess of the ether, the unused β-aminoethanol can be precipitated out. This is redissolved by adding more alcohol, and in this way the progress of the reaction may be followed.

(2.) The same dark reddish-brown solution was obtained in every experiment, seemingly independent of the solvent used and the temperature of the reaction.

D. 2,6-Dihydroxymorpholine.

1. Relation to our problem.

We first became interested in the work of Wolff and Marburg (35) because these authors reported a very similar

(34). See page 42.ff.

(35). Wolff and Marburg, Annalen, 363, 203-220 (1908).

darkening of their solutions while working with the compound 2,6-dihydroxymorpholine. This point will be discussed presently.

2,6-dihydroxymorpholine is of interest also because it would seem to offer some possibility of being converted into the corresponding dichloromorpholine. Moreover, this 2,6-dichloromorpholine would be doubly interesting to us because, theoretically at any rate, it should be possible to treat this with alcoholic potassium hydroxide and obtain oxazine.

2. Preparation.

Wolff and Marburg also used chloroacetal as a starting material. Their synthesis of 2,6-dihydroxymorpholine is as follows:
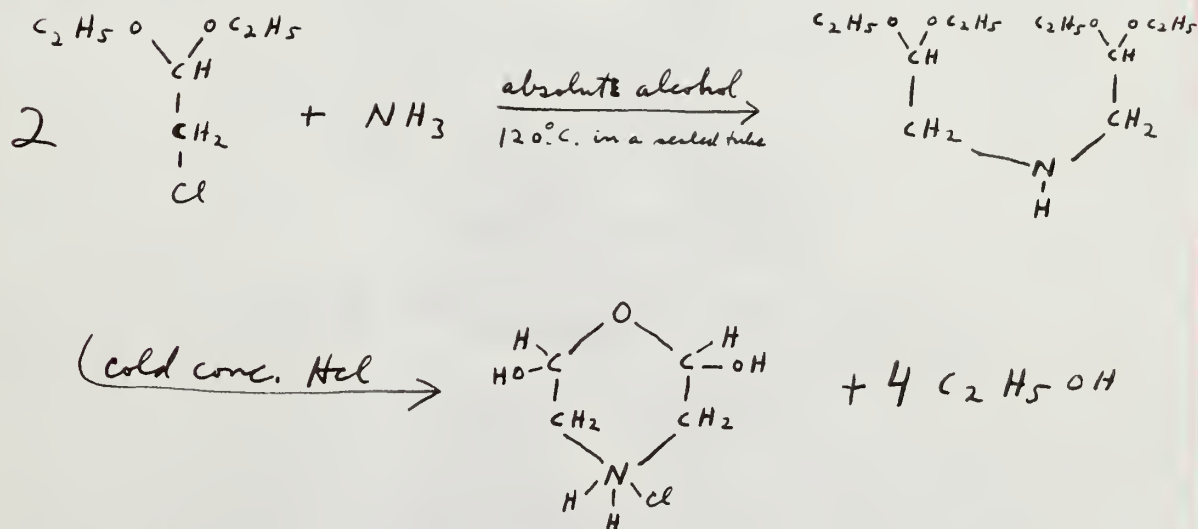
3. Properties.

This dihydroxymorpholine hydrochloride is a very interesting and surprising compound - surprising because α-hydroxyethers are notoriously unstable. Yet it is a nice white crystaline compound melting at $121 - 124^\circ$ C. A 30%

hydrochloric acid solution of this compound is stable at room temperature, but turns brown and resinifies on warming. It is slightly soluble in absolute alcohol, but its stability in this medium was not described. Its aqueous solution is acidic and remains colorless a long time at 0° C., but gradually hydrolyzes and becomes brown at 20° C. In the presence of even such weak bases as sodium carbonate, sodium acetate, and calcium carbonate, it hydrolyzes and becomes colored very rapidly so that the free dihydroxymorpholine itself could not be obtained.

    4.
        Darkening of its solutions.

        Our principal objection to preparing this compound is that its solutions are so unstable that it would doubtless be very difficult to work with. On the other hand, we seem to have run into the same problem with our proposed synthesis in connection with the dark brown solution we have obtained (36). The similarity between these dark solutions of ours and those obtained by Wolff from the decomposition of his dihydroxy-morpholine hydrochloride are striking, but the connection between these two examples is not thoroughly understood as yet.

        Wolff also could not explain the darkening of his solutions satisfactorily, but thinks this may be due to the proclivity of the compound to split in water solution and thus

(36). See page 38.

form the diacetaldehydeimine which then "goes over into an
amorphous body or may condense with itself." This same
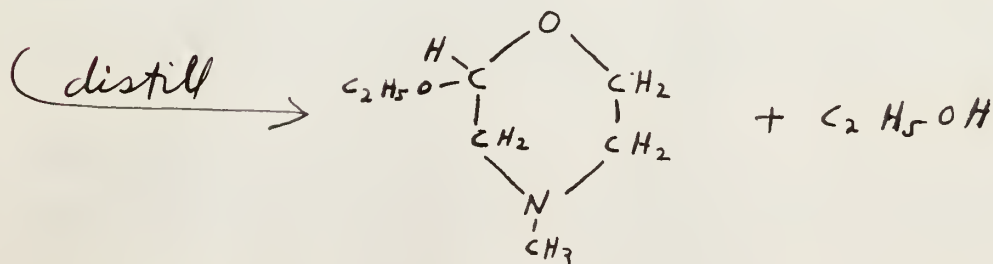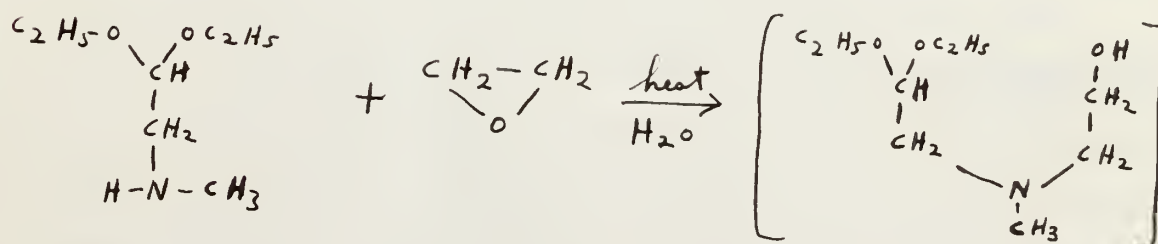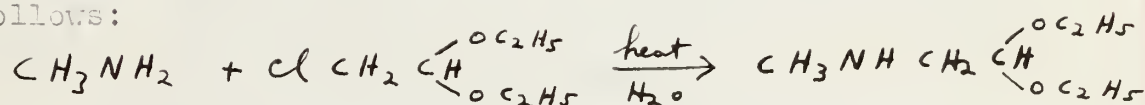explanation could be applied with equal ease to the compound

$$\begin{array}{c} C_2H_5O \\ \searrow \\ C_2H_5O \end{array} CHCH_2NHCH_2CH_2OH$$ which we have tried to prepare.

Furthermore, it was mentioned above that Wolff reported that
this darkening was greatly facilitated by the presence of
even weak alkalies, and, of course, the solutions we used
always contained an excess of β-aminoethanol and so were
always basic.

E.   2-Ethoxymorpholine.

1.   Preparation.

After our proposed Boord synthesis had been under-
taken, an experiment of Knorr's (37) was found which was
remarkably similar. The equations for Knorr's synthesis are
as follows:

$$CH_3NH_2 \ + \ ClCH_2CH \begin{array}{c} OC_2H_5 \\ \diagdown \\ OC_2H_5 \end{array} \xrightarrow[H_2O]{heat} \ CH_3NHCH_2CH \begin{array}{c} OC_2H_5 \\ \diagdown \\ OC_2H_5 \end{array}$$

$$\begin{array}{c} C_2H_5O \quad OC_2H_5 \\ \diagdown \quad \diagup \\ CH \\ | \\ CH_2 \\ | \\ H-N-CH_3 \end{array} \ + \ \begin{array}{c} CH_2-CH_2 \\ \diagdown \ \diagup \\ O \end{array} \xrightarrow[H_2O]{heat} \left[\begin{array}{cc} C_2H_5O \ \ OC_2H_5 & OH \\ \diagdown \ \diagup & | \\ CH & CH_2 \\ | & | \\ CH_2 & CH_2 \\ \diagdown_{\textstyle N} \diagup \\ | \\ CH_3 \end{array} \right]$$

$$\xrightarrow{\textit{distill}} \quad \begin{array}{c} H \quad O \\ \diagup \diagdown \quad \diagup \diagdown \\ C_2H_5O-C \qquad CH_2 \\ | \qquad\qquad | \\ CH_2 \qquad CH_2 \\ \diagdown \qquad \diagup \\ N \\ | \\ CH_3 \end{array} \ + \ C_2H_5OH$$

(37). L. Knorr, Ber., <u>32</u>, 729 (1899).

In an analogous way, 2-ethoxymorpholine was prepared:

$$C_2H_5O-\underset{\underset{\underset{NH_2}{|}}{\underset{CH_2}{|}}}{CH}-OC_2H_5 \quad + \quad \underset{O}{CH_2-CH_2} \quad \xrightarrow[\substack{12°C. \text{ for} \\ 10 \text{ hours}}]{H_2O} \quad$$
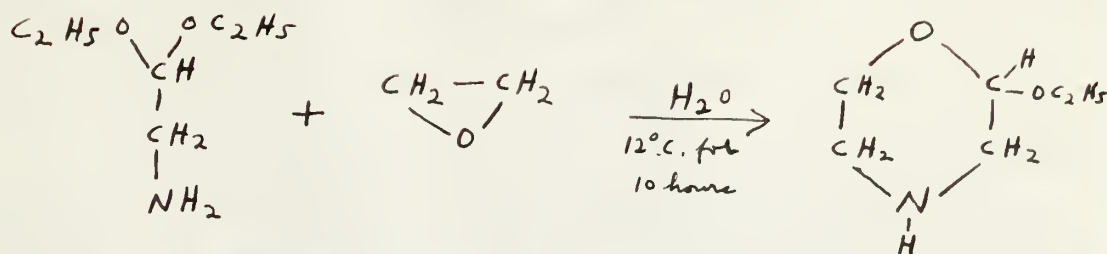
2. Relation to our problem.

It is seen that, previous to the final step, the only difference between this synthesis of Knorr's and ours is that he adds his -NHCH$_2$ CH$_2$ OH group in two steps where we tried to do this in one. In other words the same intermediate,

$$\underset{C_2H_5O}{\overset{C_2H_5O}{>}}CHCH_2NHCH_2CH_2OH$$, (38) should be obtained in both

Knorr's synthesis and ours. Hence, if our reaction between chloroacetal and β-aminoethanol described above (39) has taken place to form this intermediate, we should be able to obtain this compound of Knorr's by a simple distillation of our water solution of this iminoacetal.

Possibly, however, the fact that Knorr did not describe his 2-ethoxymorpholine or his 2-ethoxy-4-methylmorpholine or attempt to prove their structures would indicate that his yield was poor. His elementary quantitative analyses for nitrogen, carbon, and hydrogen checked very well with those calculated for these two compounds, but Knorr did not describe

(38) See page 33.
(39) See page 36.

their properties further than to say that the boiling point
of 2-ethoxymorpholine was 253°- 255°C. He also stated that the
reaction would not proceed in the absence of water.

In an attempt to see if we could obtain 2-ethoxy-
morpholine from the dark colored solution we obtained from
the reaction of β-aminoethanol and chloroacetal, we repeated
this reaction carefully carrying out the reaction in a
water solution in the presence of suspended calcium carbonate.
The purpose of the calcium carbonate was to take care of the
hydrogen chloride liberated after the manner described by
Campbell and Reed (40). Calculated molar quantities of
chloroacetal and β-aminoethanol were used, and the reaction
vessel was refluxed on a steam bath for three days.

The solution began to turn dark almost immediately
and was quite black after about one hour on the steam bath.
However, even at the end of the third day much of the chloro-
acetal layer remained, and almost 50% of the starting amount
of this was recovered. The dark brown water solution was
fractionally distilled, but the only products obtained were
water and a few drops of β-aminoethanol. The dark viscous
liquid which remained in the flask when all of the water had
been removed was insoluble in ether and could not be distilled
either at atmospheric pressure or reduced pressures, for in

(40). Campbell and Reed, Ind. Eng. Chem., 28, 656 (1936).
Also Marion C. Reed, U.S. patent 2,001,584 (1935).

both cases it merely pyrolyzed to a black solid instead of distilling.

It was found that if a few ccs. of fresh β-aminoethanol was placed in the flask after all of the water had been removed, and this mixture was then distilled at atmospheric pressure, a little of the dark liquid "steam distilled" with the β-aminoethanol.

We isolated some of the dark brown liquid in this way, and since it was too impure for an analysis, we decided to try to obtain a solid derivative of it by reacting it with the Grignard reagent, phenyl magnesium bromide. If 2-ethoxymorpholine were a constituent of this dark brown liquid, we should have expected to get the reaction

This 2-phenylmorpholine has never been prepared, but we expected it to be a solid because its isomer, 4-phenyl-morpholine, melts at 57°C.

We tried this Grignard reaction, and did obtain a reddish solid, insoluble in water, soluble in ether and alcohol, and very soluble in acetone.

It was very hard to purify and was recrystalized ten times from hot absolute alcohol, but the solid we obtained still retained a slight pinkish tinge. It had a very fragrant odor which was a bit fruity, much like that of an ester or

styrene.

However , we soon found that our solid was not 2-phenylmorpholine, for it was not at all basic as this surely would be, but was entirely neutral. Moreover, a Kjeldahl nitrogen determination showed that it contained only 2.03% of nitrogen whereas 8.59% of 2-phenyl morpholine would be nitrogen.

Hence the facts seem to point to the conclusion that the second step of our synthesis does not proceed as we had expected so that $\begin{matrix} C_2H_5O \\ C_2H_5O \end{matrix} > CH\,CH_2\,NH\,CH_2\,CH_2\,O\,H$ is not formed by the reaction of chloroacetal and β-aminoethanol. Just what does form during this reaction to give us our dark colored solution remains unknown, but it is significant in this connection that roughly two mols of the β-aminoethanol react with one mol of chloroacetal.

Part Four

Summary

Direct halogenation of morpholine and morpholine
derivatives has been attempted and found to result only in a
complete tearing down of the morpholine ring of some of these
molecules with the simultaneous formation of morpholine
hydrohalide from the unreacted molecules.

Indirect syntheses of halogenomorpholines were then
undertaken. We have tried to prepare oxazine, but have
succeeded in obtaining only traces of this compound at best.
Three different methods were tried in our attempt to prepare
oxazine, and reasons for the failure of those methods were
found. The reaction product of selenium on morpholine has been
studied.

A synthesis of chloromorpholine similar to Bourd's
synthesis of straight chain α-chloroethers has been begun,
but difficulties were met with which seem to be attributable
to an abnormal reaction between β-aminoethanol and
chloroacetal.

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